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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,600	03/11/1999	YAROM COHEN	TPP30566	7243

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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	24

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/254,600	COHEN, YAROM	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *110-115,117 and 118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *110-115,117 and 118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendments, filed 11-12-02, 1-3-03, and 3-3-03 is acknowledged. The amendments canceled claims 59-109 and 116 and amended 110, 113-115, and 118. Claims 110-115 and 117-118 are pending in this application.

Election Restriction

1. Applicant's election of Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] in Paper No. 17 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Although the Applicants did not specifically as such, the elected species reads on claims 59-62, 66, 93, 110-112 and 116. Accordingly, Claims 63-65, 67-92, 94-109 and 113-115 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 17.

2. All rejection cited in the previous office action and not cited herein, are hereby withdrawn. In light of Applicants amendment to the claims, New Grounds of rejection are cited below. Some of the art applied to these rejections were applied in the previous office action. Arguments that were raised by Applicants with regard to these references have been addressed below.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 110-115 and 117-118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mogul et al. and Reaven in view of Orskov et al. and Verber et al.

The claims are drawn to a method of treating Syndrome X to a patient exhibiting symptoms of Syndrome X by the administration of somatostatin.

Mogul et al. teach that "[h]yperinsulinemia is a manifestation of insulin resistance, a precursor to non-insulin diabetes mellitus (NIDDM) and the hallmark of Metabolic Syndrome X." (See page 4492). Reaven et al. outlines role of insulin resistance in both NIDDM patients and impaired glucose intolerance patients. The reference states that insulin resistance is not confined

to individuals with abnormal glucose tolerance and resistance to insulin stimulated glucose uptake of a degree comparable to that seen in patients with NIDDM exists in ~25% of non-obese individuals with normal oral glucose tolerance (see page 1601). The reference states that Syndrome X is marked by insulin-stimulated glucose uptake, hyperglycemia, hyperinsulinaemia. (See page 1605). The difference between the prior art and the instant application is that the reference does not teach the use of somatostatin to treat symptoms of syndrome x.

However, Orskov et al. teach the somatostatin analog octreotide improved insulin stimulated glucose disposal and increased the suppressive effect of insulin on the liver, indicated improvement of insulin sensitivity (see page 215). GH has been shown to decrease insulin sensitivity both in the liver and in peripheral tissues and the suppression of GH levels is probably at lease partly responsible of the improved insulin sensitivity following octreotide (see page 215). In previous studies using Octreotide, it had been demonstrated that glucose metabolism and insulin sensitivity had both been improved using a higher dosage of the analog (see page 215). The reference concludes the octreotide infusion decreased insulin requirement and increased insulin sensitivity in IDDM patients (see page 215).

Veber et al teaches that the cyclic peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] is 50 to 100 times more potent than somatostatin for the inhibition of insulin, glucagon, and growth hormone release (see abstract). The reference states that the cyclic somatostatin analog enhances the ability of insulin to control blood glucose when administered to diabetic animals (see page 1377). Finally, the cyclic analog has a slow metabolism and thus has a longer half life in vivo (see page 1377). The reference also teaches that the somatostatin analog was given in the dosage of 50μg (see page 1376).

Therefore, since the art recognizes that insulin resistance is the hallmark of Syndrome X, it would have been obvious to use somatostatin to control insulin resistance, and thereby treat Syndrome X. One would have been motivated to use somatostatin because somatostatin has been shown to treat insulin resistance in diabetic patients. It would have been further obvious to use the peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] instead of native somatostatin to treat insulin resistance because this somatostatin analogue has been shown to be 50 to 100 time more potent than somatostatin and since this somatostatin analog has a longer half life.

Arguments

In the response dated, 11-12-02, Applicants stated that none of the cited references describes the treatment presently claimed because none of the references relate to the treatment of Syndrome X of Reaven. Applicants contend that the references are concerned with the treatment of diabetes with somatostatin and Syndrome X and Type II diabetes are distinct medical conditions. Applicants conclude that "because somatostatin [sic] and its derivatives may be useful in the treatment of insulin deficiency, at best, these reference teach that somatostatin may be used as a research tool for investigating its effectiveness with respect to other diseases the symptoms of which include insulin deficiency. However, such an analysis is deemed 'obvious to try' and may not be the basis of an obviousness rejection under 35 USC § 103(a)."

In the response dated 1-3-03, Applicants stated "[e]ven if insulin resistance is a symptom of Syndrome X and the reference teach that somatostatin derivatives are useful in treating insulin resistance, Applicants respectfully submits that it would not necessarily have been obvious to use the compounds recited by claim 10, as the cited references do not relate to, nor identify Syndrome X." Applicants state it is only Applicants assumption that claimed treatment functions via the

reduction of insulin resistance, but it is possible that the treatment actually function in a different manner. Applicants state that "it is generally known that the treatment of a single symptom does not deal with all aspects of a particular disease or problem. In other words, treatment of an individual symptom is not necessarily an equivalent to treatment of a particular disease or condition."

Response to Arguments

3. Applicant's arguments filed 11-12-02 and 1-3-03 have been fully considered but they are not persuasive.

On page 2 of the specification it is stated:

> "All of the risk factors of syndrome X of Raven are, inter alia, caused by a high resistance to Insulin. Thus, apparently said symptoms could be treated simultaneously if there would be reduction of the resistance to Insulin. . . We have now found that due to the **fact** that the reduction of the resistance to Insulin can be achieved by administration of a compound selected among somatostatin or its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined and metformin, said treatment may enable the treatment of all risk factors of syndrome X of Reaven simultaneously."

These two paragraphs, taken from Applicants, specification supply more than a mere assumption of activity as Applicants have claimed. These two paragraphs assertively conclude that there is a linkage between syndrome X and reduction of insulin resistance. These sentences, like the entire specification, establish that if one of ordinary skill in the art can reduce insulin resistance, the symptoms of syndrome X of Ravean can be treated simultaneously.

Moreover, Raeven implies that the mechanism of the insulin resistance in NIDDM patients and those with Syndrome X are very similar. Indeed, the art recognizes that Syndrome X is a

precursor to NIDDM. Thus, it would have been obvious that therapeutic methods useful in the treatment of diabetes would also be useful in treating Syndrome X. Accordingly, unlike Applicants contentions, the analysis used in the rejection is not obvious to try.

5. Claims 110-115 and 117118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reaven in view of Carretta et al. and Verber et al.

The claims are drawn to a method of treating Syndrome X to a patient exhibiting symptoms of Syndrome X by the administration of Somatostatin.

The reference of Mogul et al. and Raeven et al. have been discussed supra. Reaven et al. also teaches that hypertension is a symptom of Syndrome X (see page 1605). Further, the reference indicates that hypertension is a result of insulin resistance and hyperinsulinaemia (see page 1603-1604). The difference between the prior art and the instant application is that the reference does not teach the use of somatostatin the treatment of Syndrome X.

However, Carretta et al. illustrates that hypertension can be treated with exogenous somatostatin infusion (see abstract). The reference indicates that obese hyperinsulinaemia patients, when given somatostatin, blood pressure was significantly reduced and was maintained for 8 hours during the study (see page 3198).

Veber et al teaches that the cyclic peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] is 50 to 100 times more potent than somatostatin for the inhibition of insulin, glucagon, and growth hormone release (see abstract). The reference states that the cyclic somatostatin analog enhances the ability of insulin to control blood glucose when administered to diabetic animals (see page 1377). Finally, the cyclic analog has a slow metabolism and thus has a longer half life in vivo (see

page 1377). The reference also teaches that the somatostatin analog was given in the dosage of 50μg (see page 1376).

Therefore treat Syndrome X, specifically treating hypertension as a result of hyperinsulinaemia, using somatostatin. One would have been motivated to use somatostatin because somatostatin has been shown to treat hypertension as a result of hyperinsulinaemia. It would have been further obvious to use the peptide Cyclo [N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe] instead of native somatostatin to treat insulin resistance because this somatostatin analogue has been shown to be 50 to 100 time more potent than somatostatin and since this somatostatin analog has a longer half life.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
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